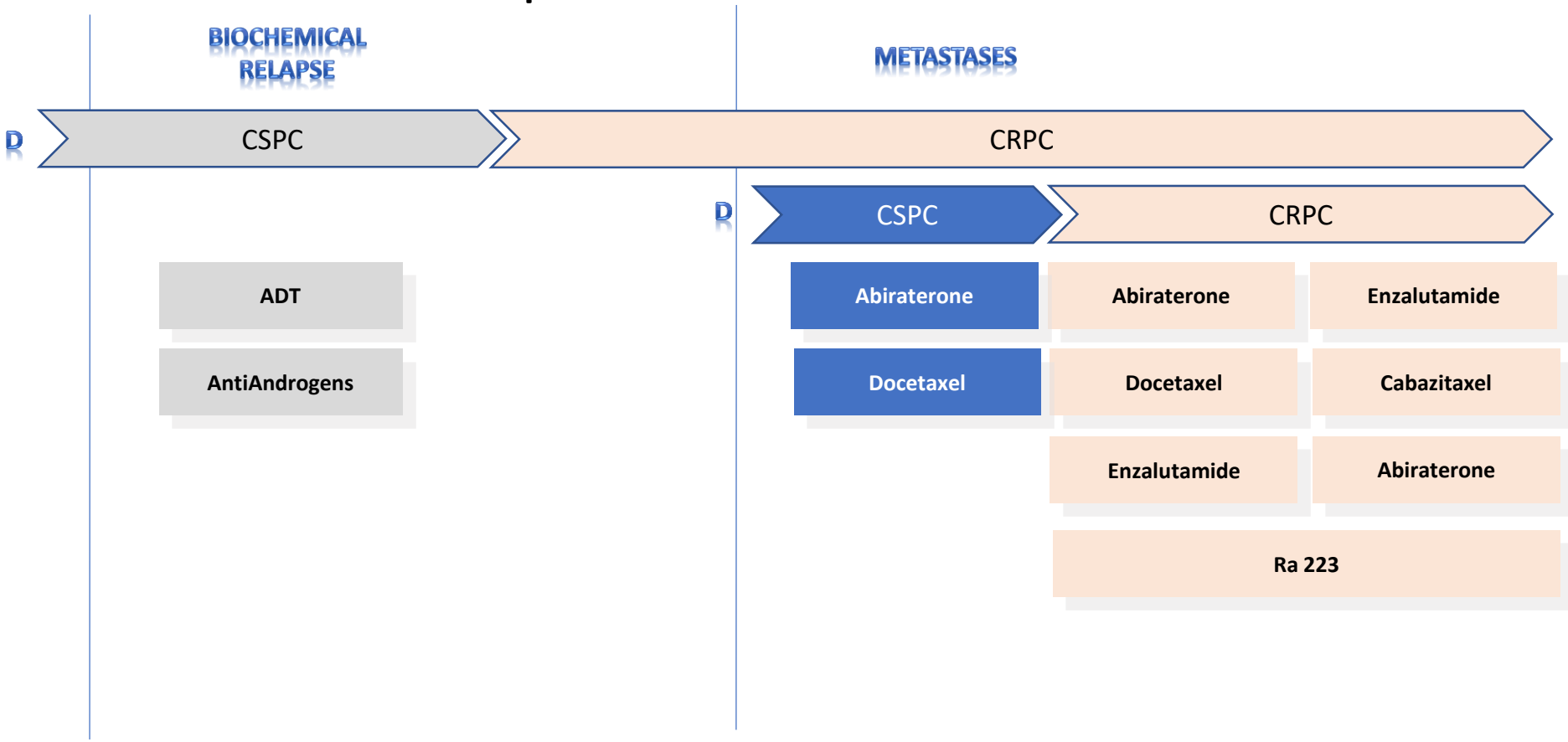
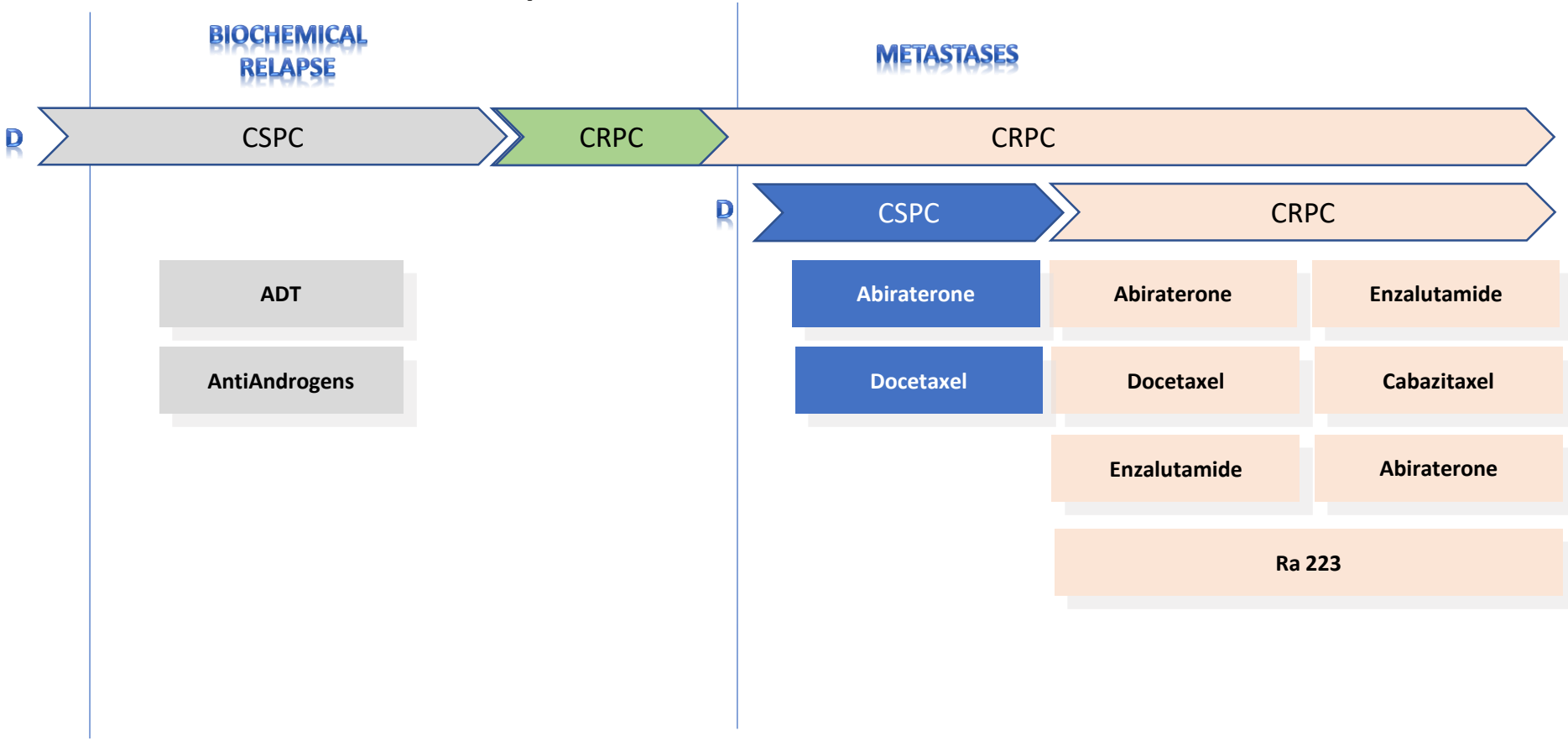
The role of early hormonal manipulation and immunotherapy in CRPC

Orazio Caffo
Medical Oncology Dept. Trento

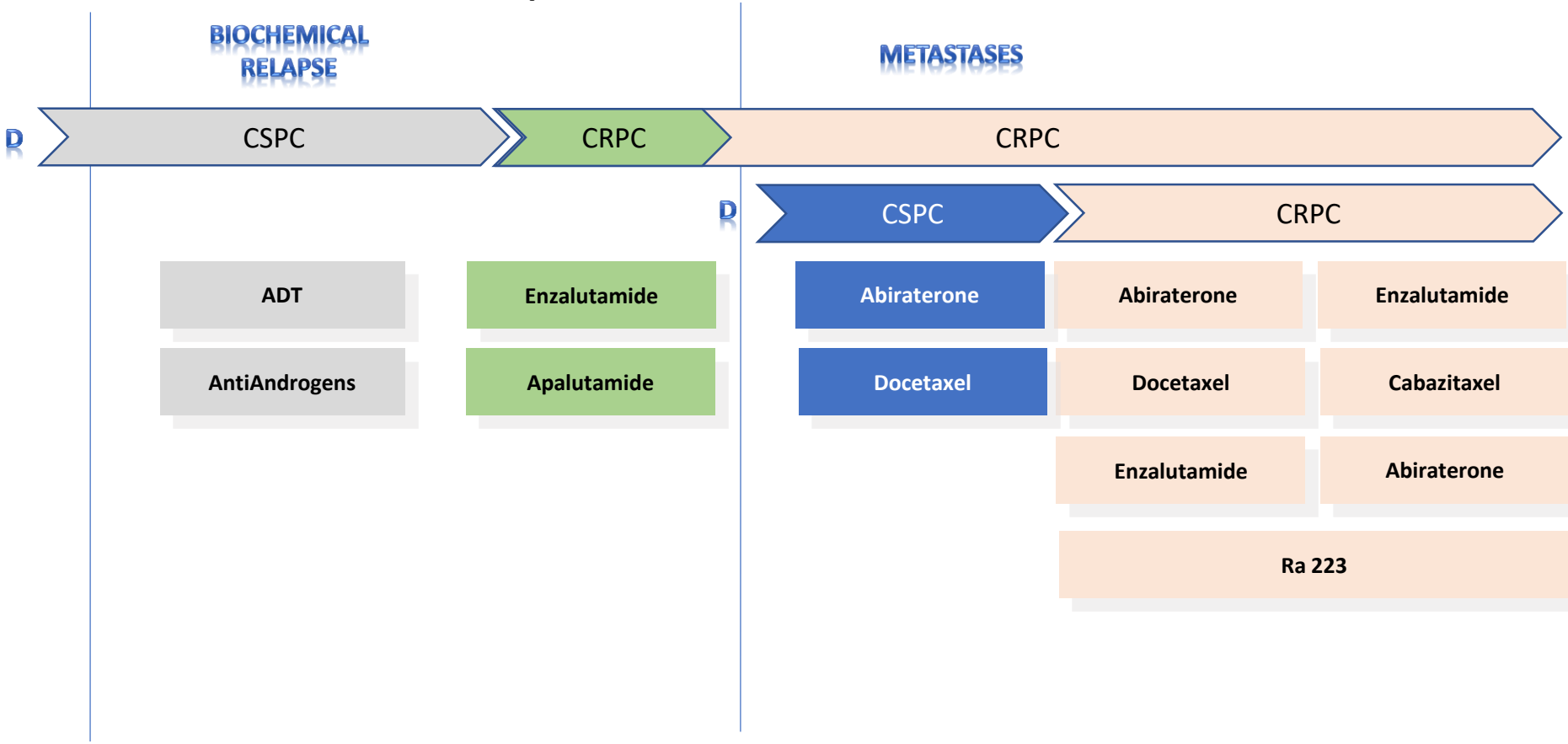
The landscape before ASCO GU 2018

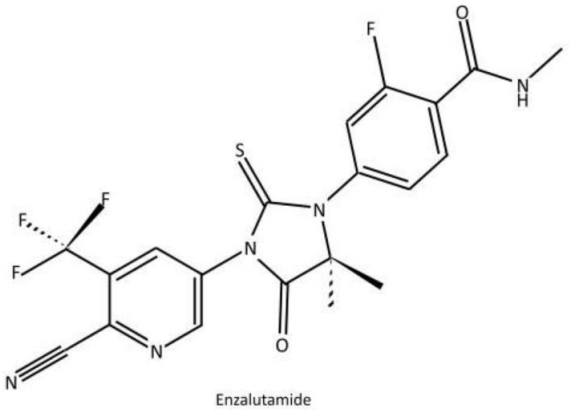


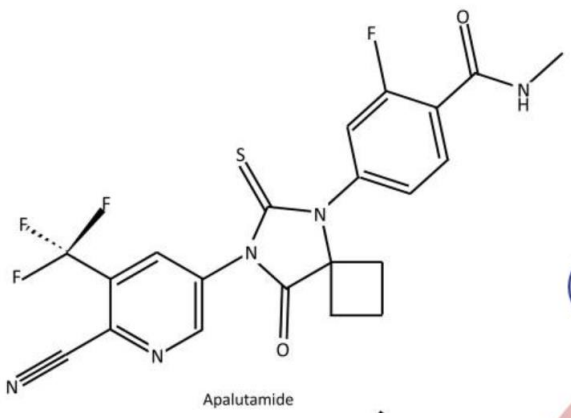
The landscape before ASCO GU 2018



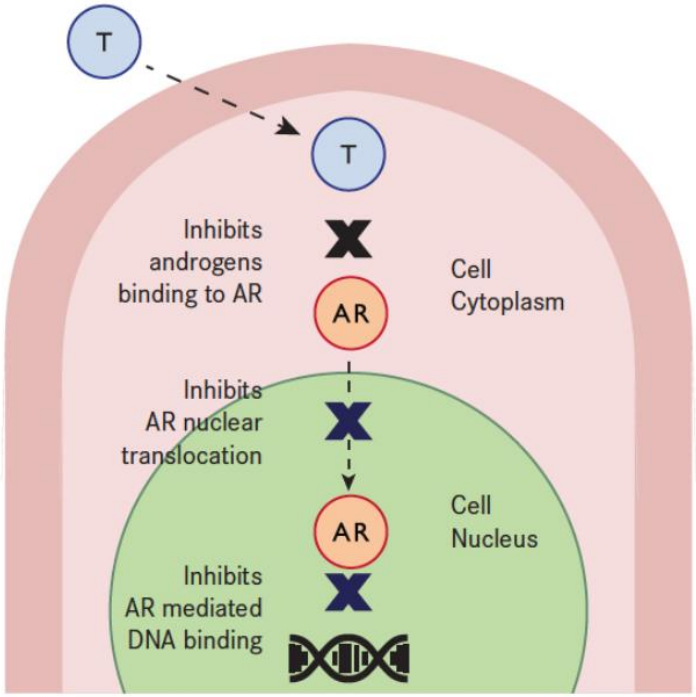
The landscape at ASCO GU 2018

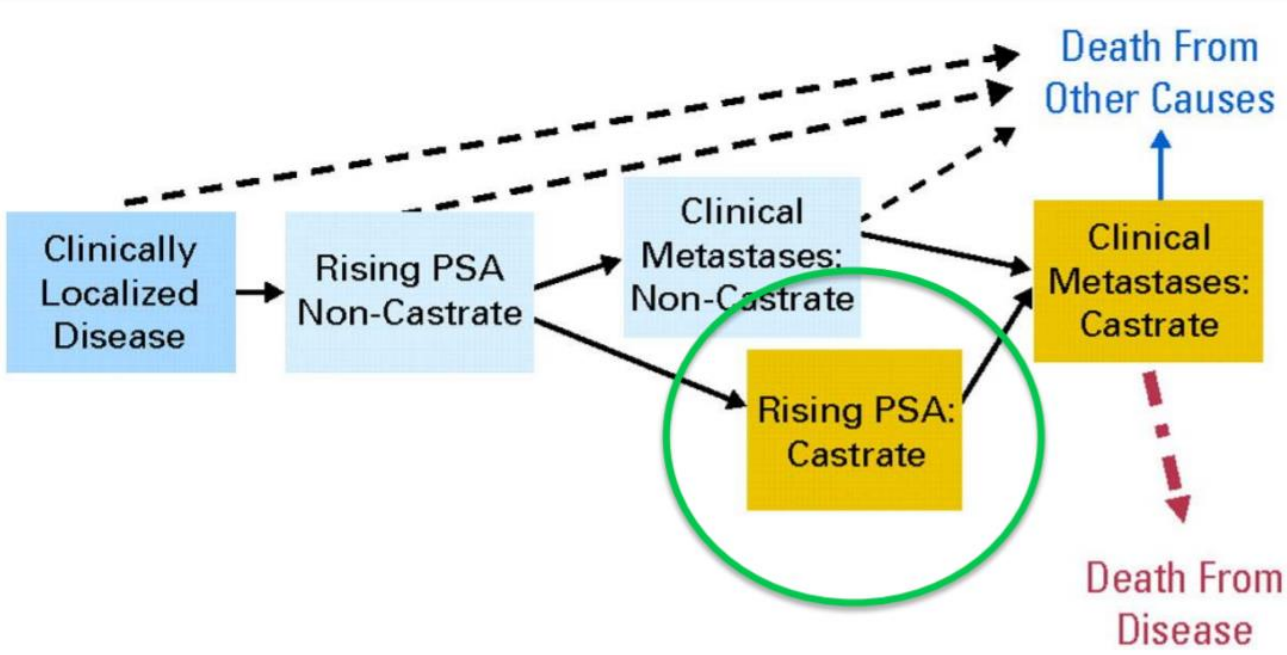


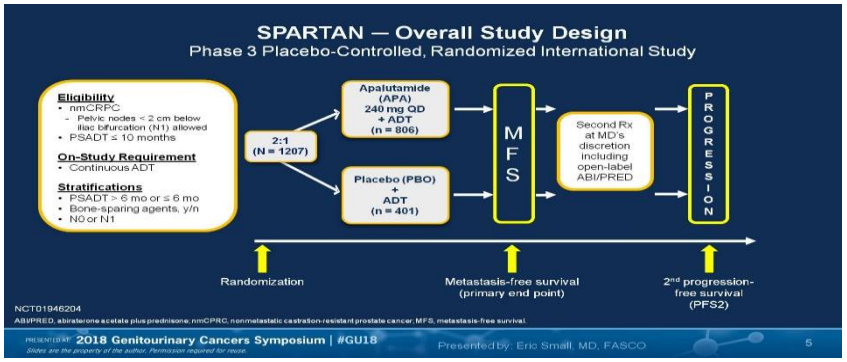


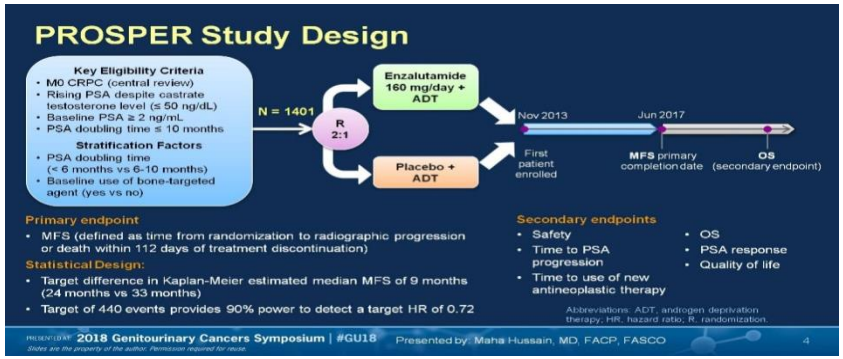


One specific concern in the clinical development of ENZ was the induction of seizures in patients with a predisposition, which is thought to be secondary to binding of GABA-A receptors in CNS.
With a lower efficacious dose (and subsequently lower levels of drug present in the CNS) a potential advantage of APA is reduced risk of seizures.




Death From
Other Causes
Clinically
Localized
Disease
Rising PSA
Non-Castrate
Clinical
Metastases:
Non-Castrate
Clinical
Metastases:
Castrate
Rising PSA:
Castrate
Death From
Disease





	SPARTAN	PROSPER
Agent Tested	Apalutamide (APA)	Enzalutamide (ENZA)
Inclusion Criteria	• cM0 cN0-1 CRPC • PSA doubling time ≤ 10 mo	• cM0N0 CRPC • PSA doubling time ≤ 10 mo • PSA ≥ 2 ng/mL
Study Design	2:1 APA/Placebo randomization	2:1 ENZA/Placebo randomization
Endpoints	Primary: Metastases-free survival (MFS) Secondary: • Time to metastases • Progression-free survival • Time to symptomatic progression • OS • Second progression-free survival (PFS2) after receiving subsequent abiraterone	Primary: Metastases-free survival (MFS) Secondary: • Time to PSA progression • Time to first use of new antineoplastic therapy • OS
Total Number of Patients	1207	1401

Primary End Point: Metastasis-Free Survival

72% risk reduction of distant progression or death

	SPARTAN	PROSPER
MFS (exp arm)	40.5 mos	36.6 mos
HR	0.28	0.29
MFS improvement	24.3 mos	21.9 mos

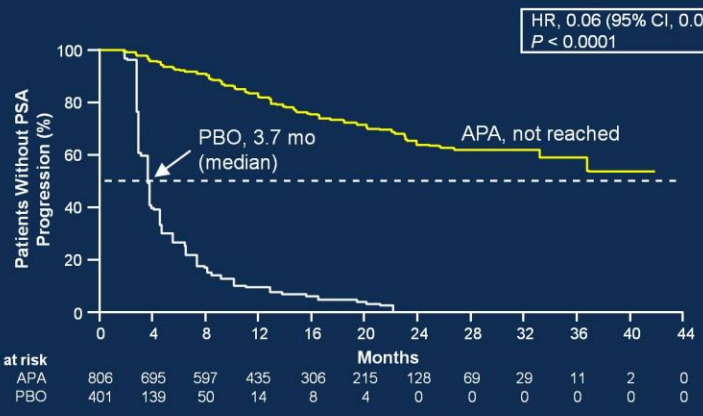
Primary Endpoint: MFS

- Median MFS was ≈ 22 months longer with enzalutamide than with placebo (71% reduction in relative risk of radiographic progression or death)

Abbreviations: CI, confidence interval; ENZA, enzalutamide; NR, not reached; PBO, placebo.

Time to PSA Progression

94% risk reduction in PSA progression



No. at risk												
APA	806	695	597	435	306	215	128	69	29	11	2	0
PBO	401	139	50	14	8	4	0	0	0	0	0	0

Time to PSA Progression

	ENZA + ADT (n = 933)	PBO + ADT (n = 468)
Median (95% CI), mo	37.2 (33.1-NR)	3.9 (3.8-4.0)
HR (95% CI)	0.07 (0.05-0.08)	
P value	< .0001	

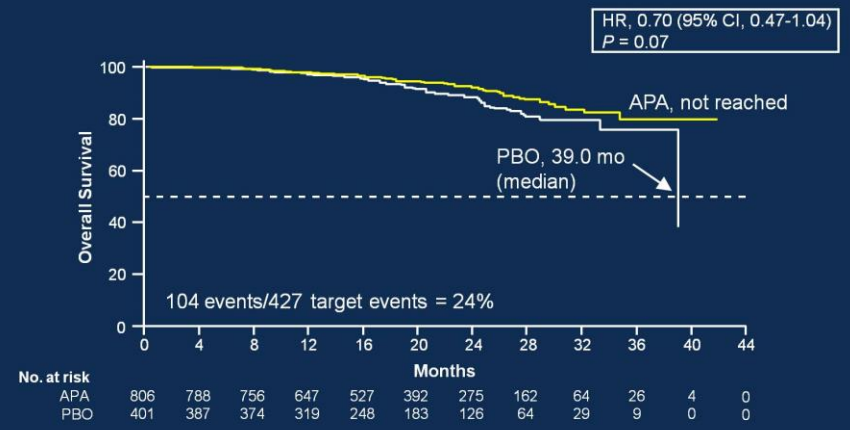
No. at risk															
ENZA + ADT	933	879	771	635	500	401	386	288	203	137	76	71	24	2	0
PBO + ADT	468	427	138	56	25	13	13	5	4	3	0	0	0	0	0

- Median time to PSA progression was ≈ 33 months longer with enzalutamide than with placebo (93% relative risk reduction)

Time to PSA progression	NR vs. 3.7 mo placebo HR 0.06, p < 0.0001	37.2 mo vs 3.9 mo placebo HR 0.07, p< .0001
Progression-free survival	40.5 mo vs. 14.7 mo placebo HR 0.29, p <0.0001	N/A
Time to symptomatic progression	Not reached HR 0.45, p<0.0001	N/A
Time to subsequent therapy	N/A	39.6 mo vs 17.7 mo placebo HR 0.21, p< .0001
OS	Interim analysis: Not reached vs. 39 months HR 0.70, p=0.07	Interim analysis: Not reached HR = 0.80 (favoring ENZA); p = 0.1519
Secondary PFS	Not reached vs. 39 months HR 0.49, p<0.0001	N/A

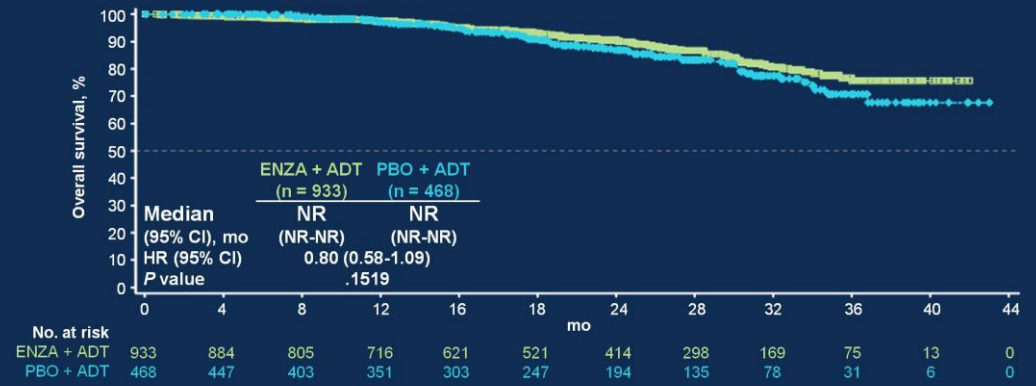
Secondary End Point: Overall Survival

30% risk reduction of death



Presented by: Eric Small, MD, FASCO

Overall Survival: First Interim Analysis



- Median follow-up time was ≈ 22 months for each treatment arm
- There was a 20% reduction in the relative risk of death with enzalutamide vs placebo

Presented by: Maha Hussain, MD, FACP, FASCO

Results: Treatment Associated Adverse Events

	APA (n = 803)		PBO (n = 398)	
	All	Gr 3/4	All	Gr 3/4
Fatigue	30.4%	0.9%	21.1%	0.3%
Rash	23.8%	5.2%	5.5%	0.3%
Weight loss	16.1%	1.1%	6.3%	0.3%
Arthralgia	15.9%	0	7.5%	0
Fall	15.6%	1.7%	9.0%	0.8%
Fracture	11.7%	2.7%	6.5%	0.8%
Hypothyroidism	8.1%	0	2.0%	0
Seizure	0.2%	0	0	0

Adverse Events*

Event, No. (%)	Enzalutamide + ADT (n = 930)	Placebo + ADT (n = 465)
Any adverse event	808 (87%)	360 (77%)
Any grade ≥ 3 adverse event	292 (31%)	109 (23%)
Grade ≥ 3 adverse events occurring in ≥ 1% of patients in the enzalutamide group		
Hypertension	43 (5%)	10 (2%)
Fatigue	27 (3%)	3 (1%)
Hematuria	16 (2%)	13 (3%)
Fall	12 (1%)	3 (1%)
Asthenia	11 (1%)	1 (< 1%)
Pneumonia	10 (1%)	2 (< 1%)
Syncope	10 (1%)	2 (< 1%)
Anemia	9 (1%)	6 (1%)
Urinary tract infection	7 (1%)	3 (1%)
Cataract	7 (1%)	2 (< 1%)
Cardiac failure	7 (1%)	1 (< 1%)
Acute myocardial infarction	6 (1%)	2 (< 1%)
Adenocarcinoma of the colon	5 (1%)	2 (< 1%)
Hyperglycemia	5 (1%)	1 (< 1%)
Hyponatremia	5 (1%)	1 (< 1%)
Coronary artery disease	5 (1%)	0

Adverse events as the primary reason for treatment discontinuation:

- Enzalutamide, n = 87 (9%)
- Placebo, n = 28 (6%)

Deaths due to adverse event on trial irrespective of attribution:

- Enzalutamide, n = 32 (3%)
- Placebo, n = 3 (1%)

*Adverse events were collected up to 30 days after the last dose of study drug.

Adverse Events of Special Interest*

Any Grade Event, No. (%)	Enzalutamide + ADT (n = 930)	Placebo + ADT (n = 465)
Hypertension†	114 (12%)	25 (5%)
Major adverse cardiovascular event‡	48 (5%)	13 (3%)
Mental impairment disorders§	48 (5%)	9 (2%)
Hepatic impairment	11 (1%)	9 (2%)
Neutropenia	9 (1%)	1 (< 1%)
Convulsion	3 (< 1%)	0
Posterior reversible encephalopathy syndrome	0	0

In both arms the incidence of major adverse cardiovascular events was higher in patients with:

- Baseline history of cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, or age ≥75 years

*Adverse events were collected up to 30 days after the last dose of study drug.
†Includes increased blood pressure.
‡Includes acute myocardial infarction, hemorrhagic cerebrovascular conditions, ischemic cerebrovascular conditions, and heart failure.
§Includes memory impairment, disturbance in attention, cognitive disorders, amnesia, dementia Alzheimer's type, senile dementia, mental impairment, and vascular dementia.

Progression Event by Type

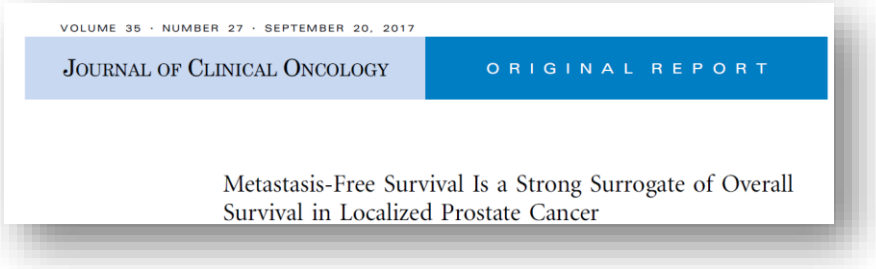
Event, No. (%)	Enzalutam… (n =	
All progression events*	**219 (**	
Radiographic progression†	187 (8	
New bone metastases	71 (32	
New soft-tissue metastases	109 (50%	
Concurrent new bone and soft-tissue metastases	7 (3%)	
Death without documented radiographic progression within 112 days of study treatment discontinuation†	32 (15%)	4 (2%)

- The proportion of progression events in the enzalutamide arm was 50% less than that of the placebo arm

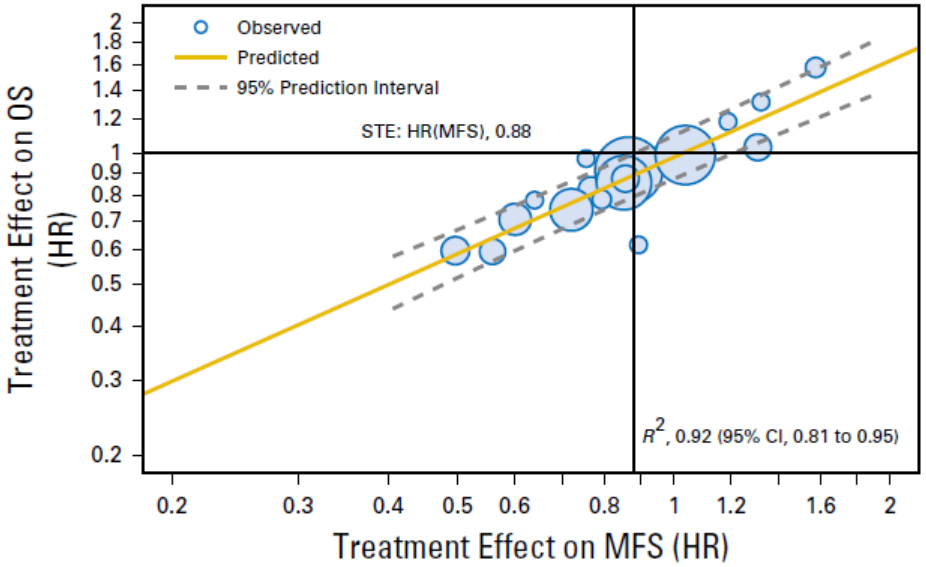
*Event percentages are based on total number of patients randomized in each arm (enzalutamide + ADT, n = 933; placebo + ADT, n = 468)
†Partition of event percentages are based on total number of events in each arm (enzalutamide + ADT, n = 219; placebo + ADT, n = 228).

Open questions

- Is MFS an appropriate endpoint?

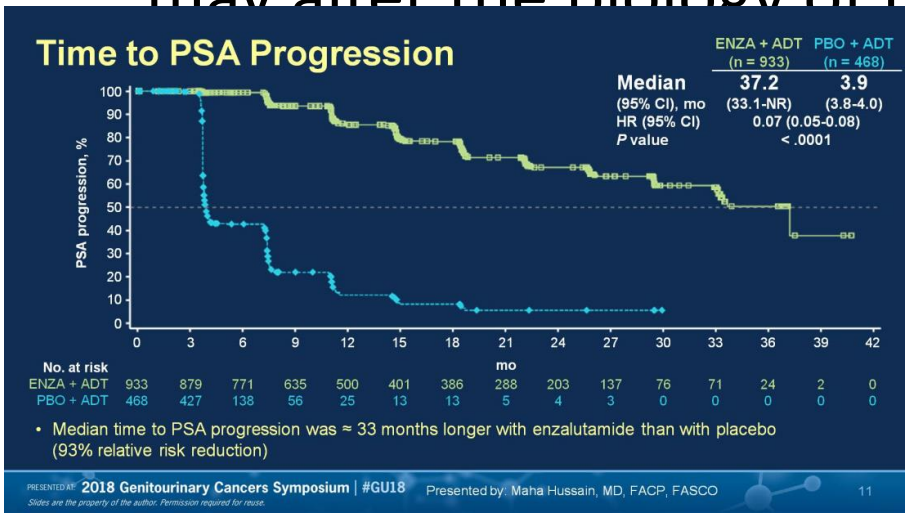

VOLUME 35 · NUMBER 27 · SEPTEMBER 20, 2017
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

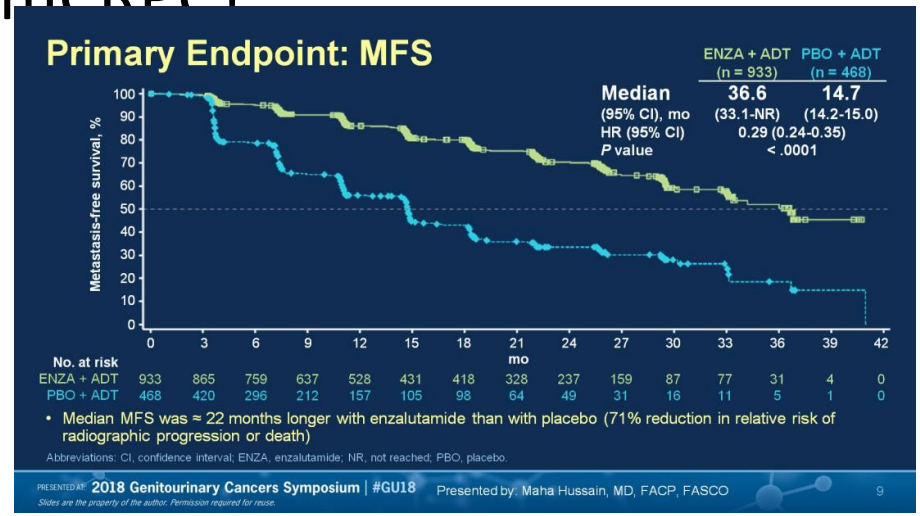
Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer



Open questions

- Is PSA a reliable predictor of disease progression during APA/ENZ treatment?
- Does the impact on PSA suggest that these agents may alter the biology of nmCRPC?





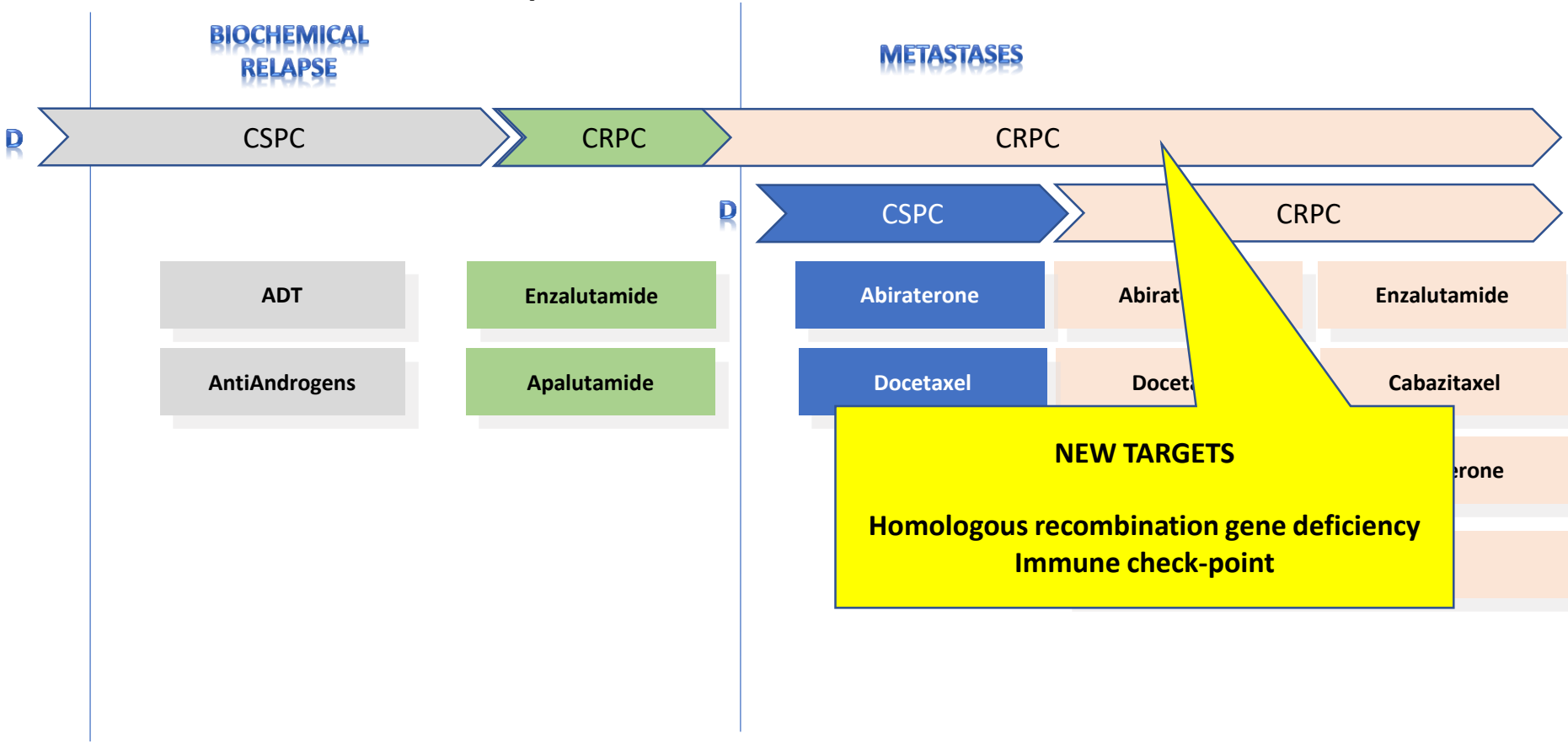
Open questions

- Should the toxicity profile temper the enthusiastic feelings about the disease control improvement?
- Could confidence in these agents be greater if understanding of the side effects will be better?

Open questions

- The trials used conventional imaging approach, with CT scans and bone scans: could more recent imaging techniques (fluciclovine PET, PSMA PET) potentially able to earlier detect metastases, shrink the population of men with nmCRPC?

The landscape at ASCO GU 2018



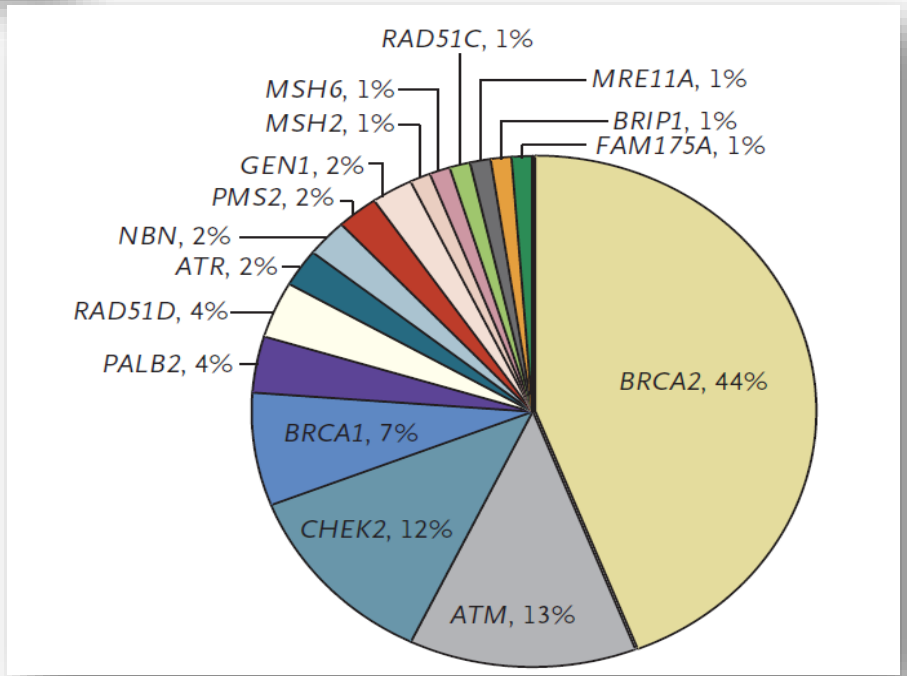
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

N Engl J Med 2016;375:443-53.

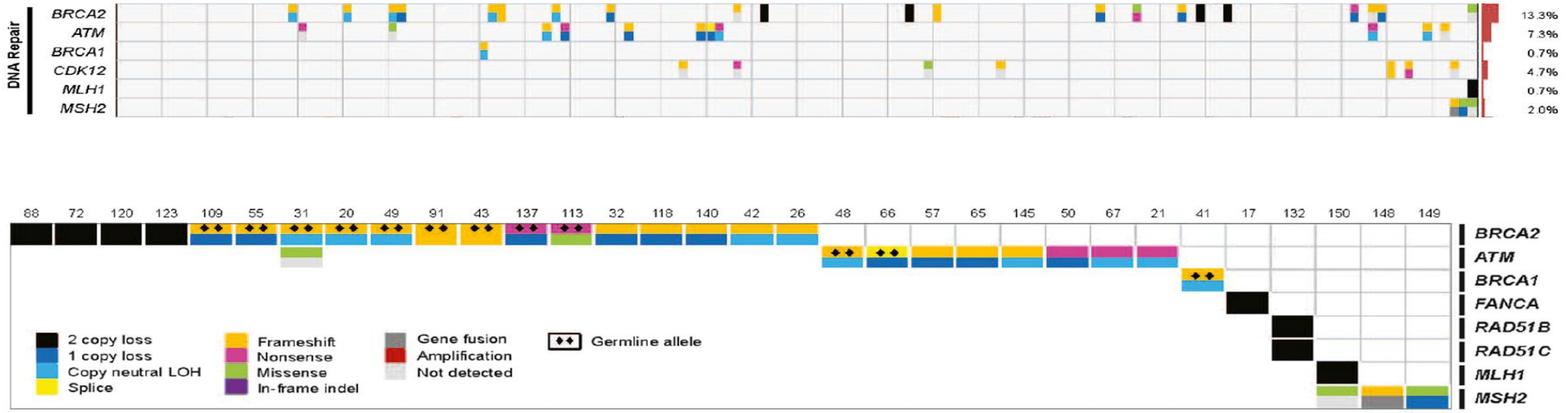
- 692 pts
- 82 (11.8%) at least one presumed pathogenic germline mutation in a gene involved in DNA-repair processes
- 16 different genes [BRCA2 (37 mutations)]



Resource

Cell

Integrative Clinical Genomics of Advanced Prostate Cancer



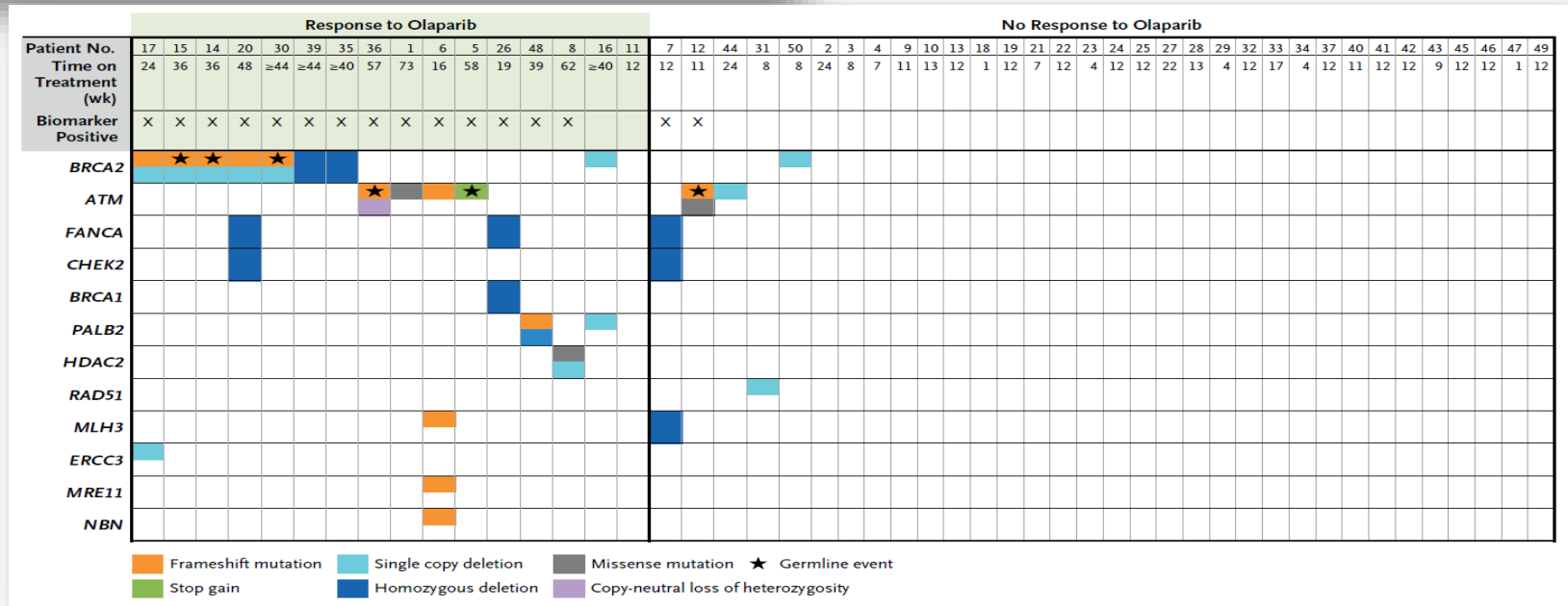
Robinson Cell 2015

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono

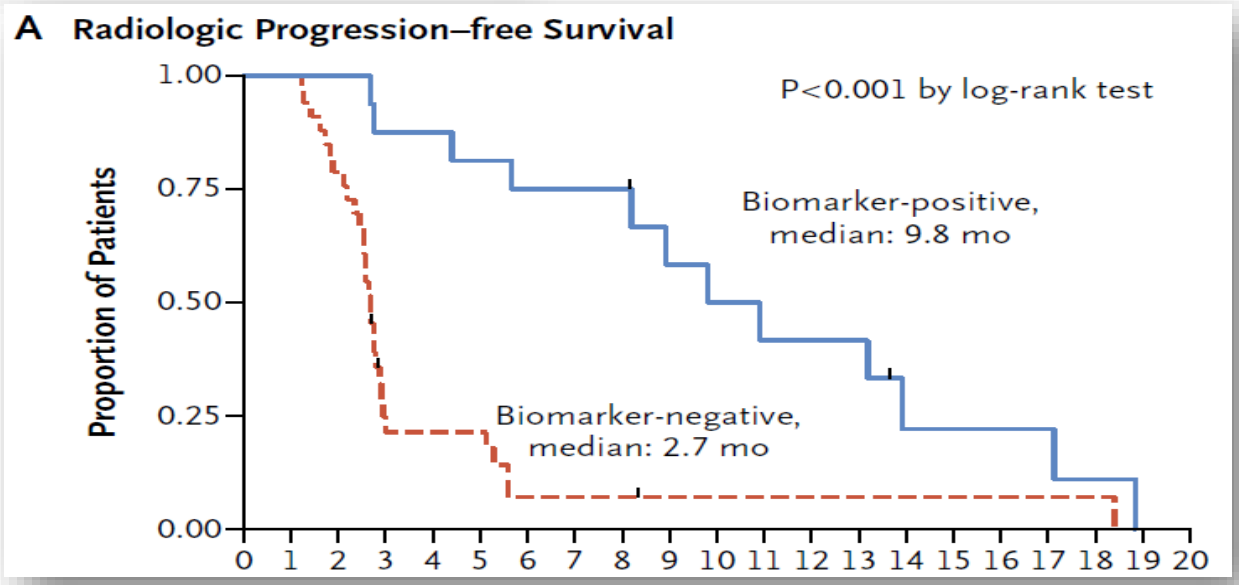


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono

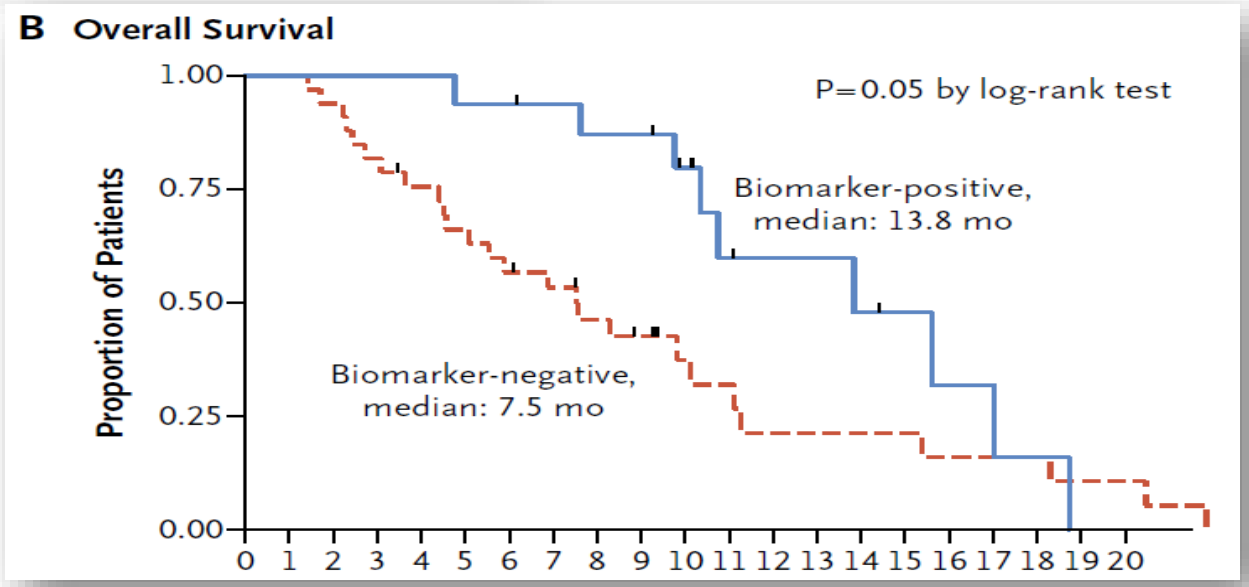
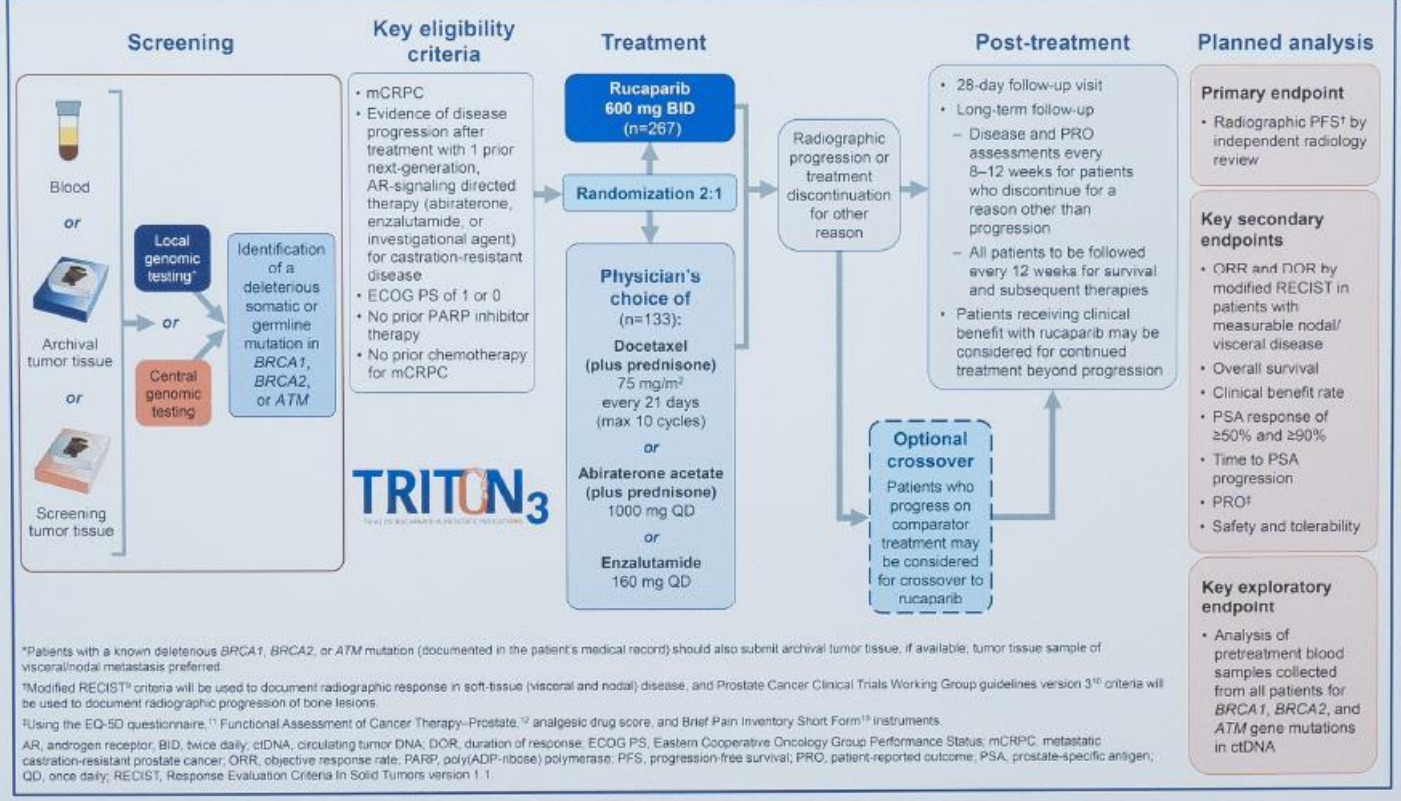


Figure 2. TRITON3 Trial Schema



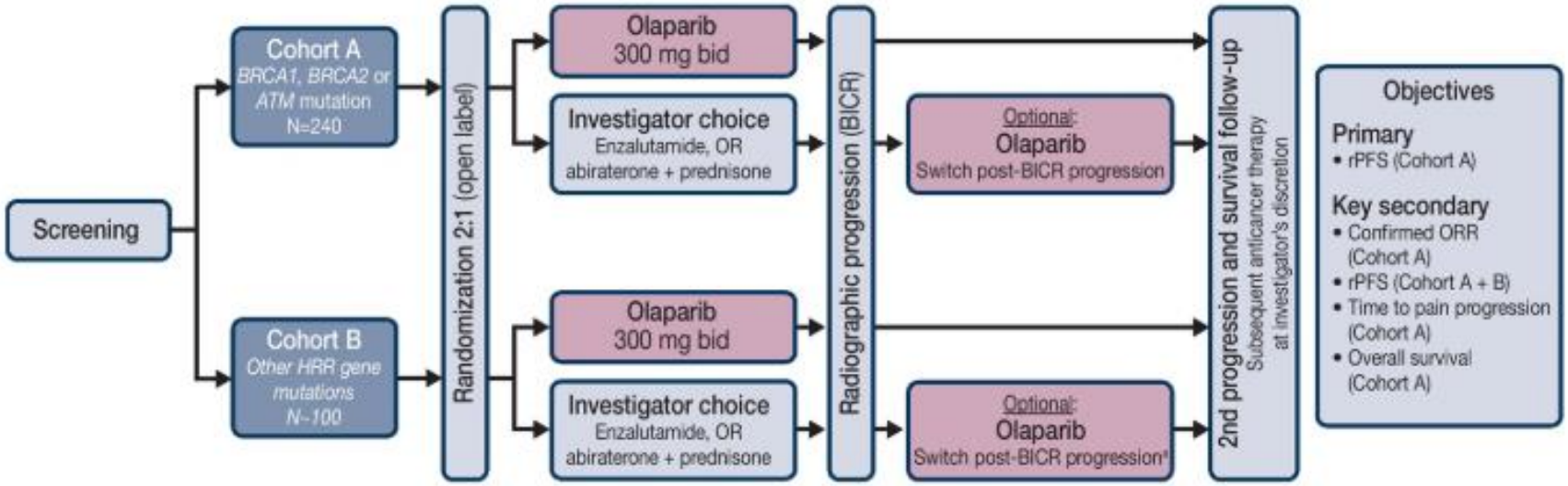
*Patients with a known deleterious *BRCA1*, *BRCA2*, or *ATM* mutation (documented in the patient's medical record) should also submit archival tumor tissue, if available; tumor tissue sample of visceral/nodal metastasis preferred.

†Modified RECIST[9] criteria will be used to document radiographic response in soft-tissue (visceral and nodal) disease, and Prostate Cancer Clinical Trials Working Group guidelines version 3[10] criteria will be used to document radiographic progression of bone lesions.

‡Using the EQ-5D questionnaire,[11] Functional Assessment of Cancer Therapy–Prostate,[12] analgesic drug score, and Brief Pain Inventory Short Form[13] instruments.

AR, androgen receptor; BID, twice daily; ctDNA, circulating tumor DNA; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; PRO, patient-reported outcome; PSA, prostate-specific antigen; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Figure 3. PROfound study design



Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial

Lancet Oncol 2018

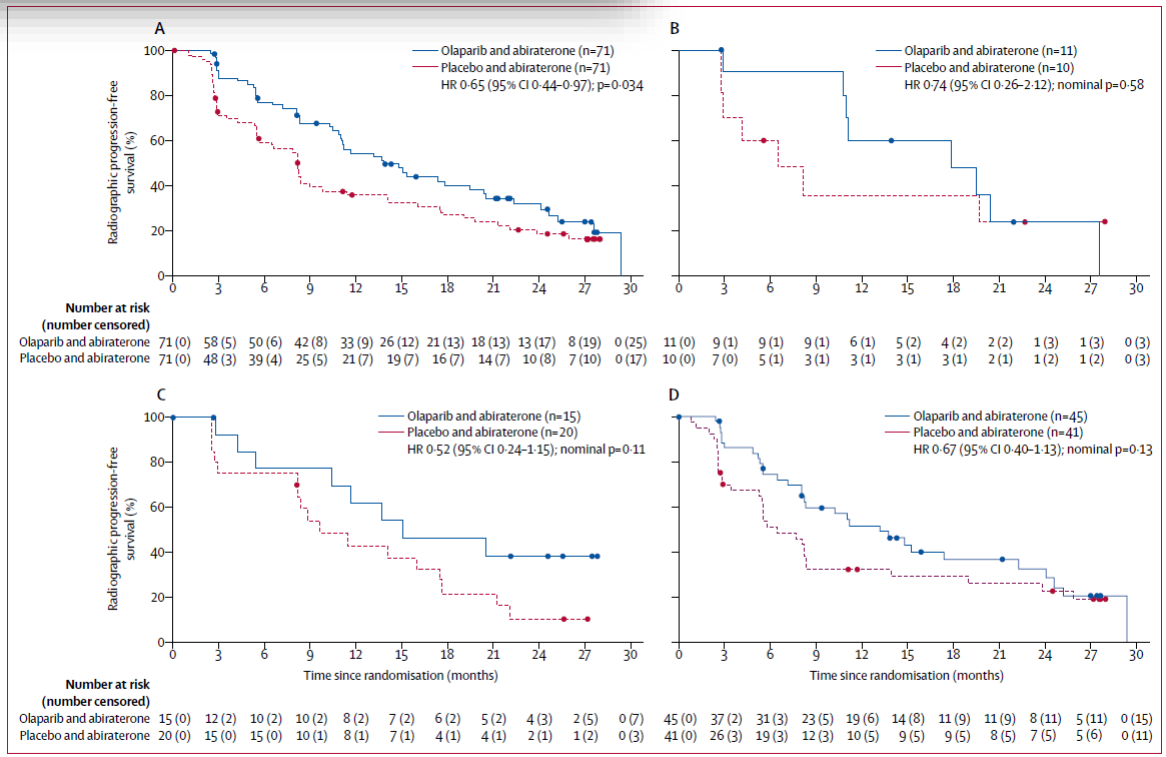
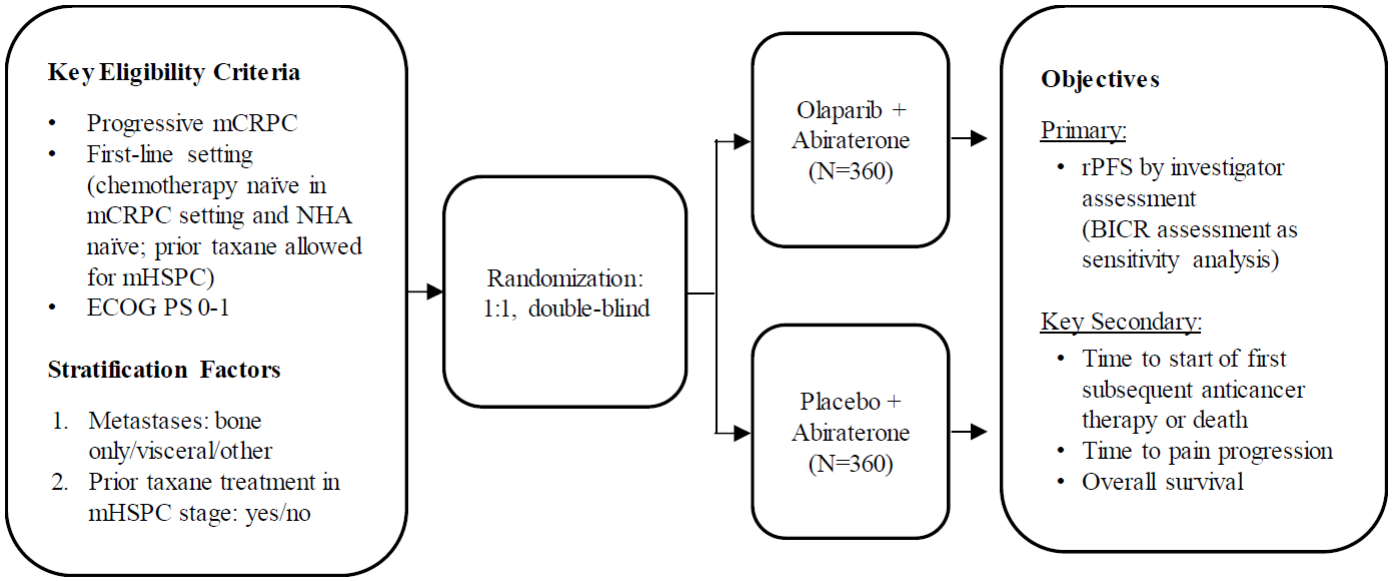
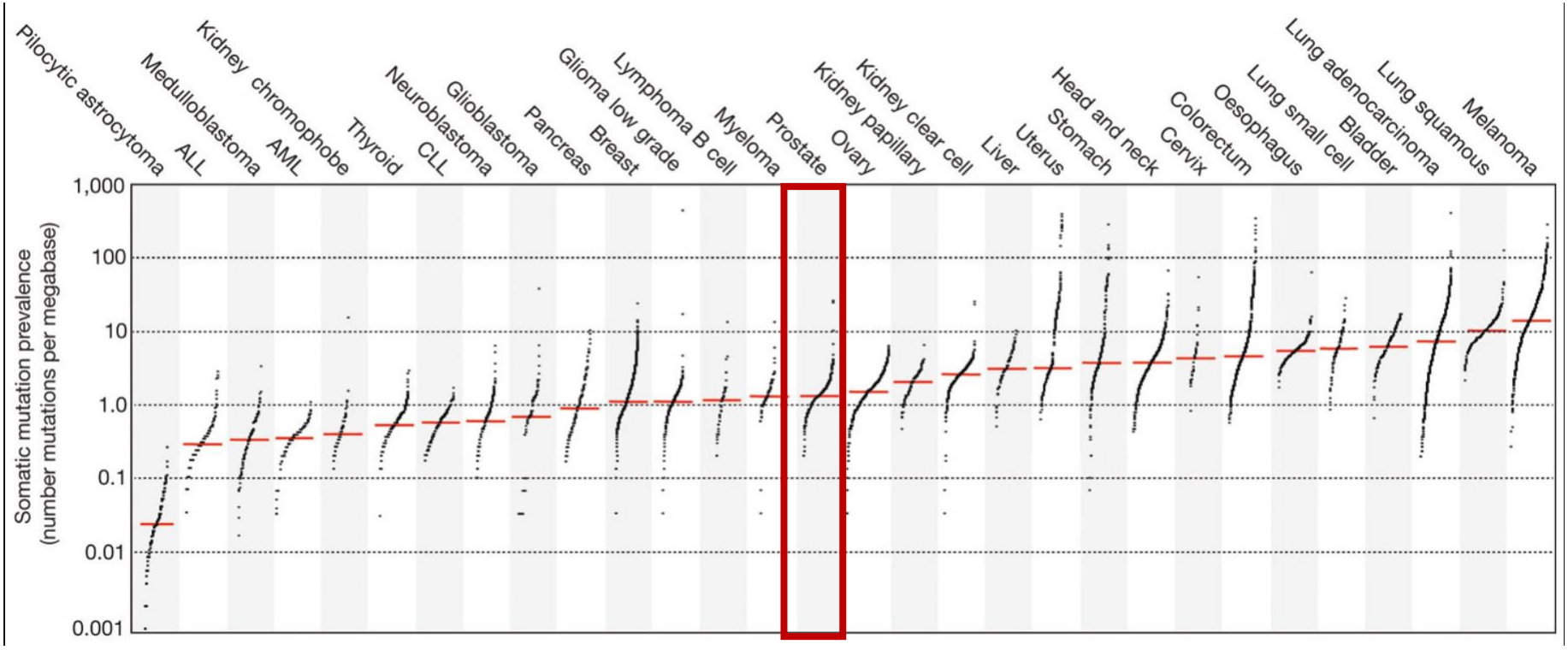
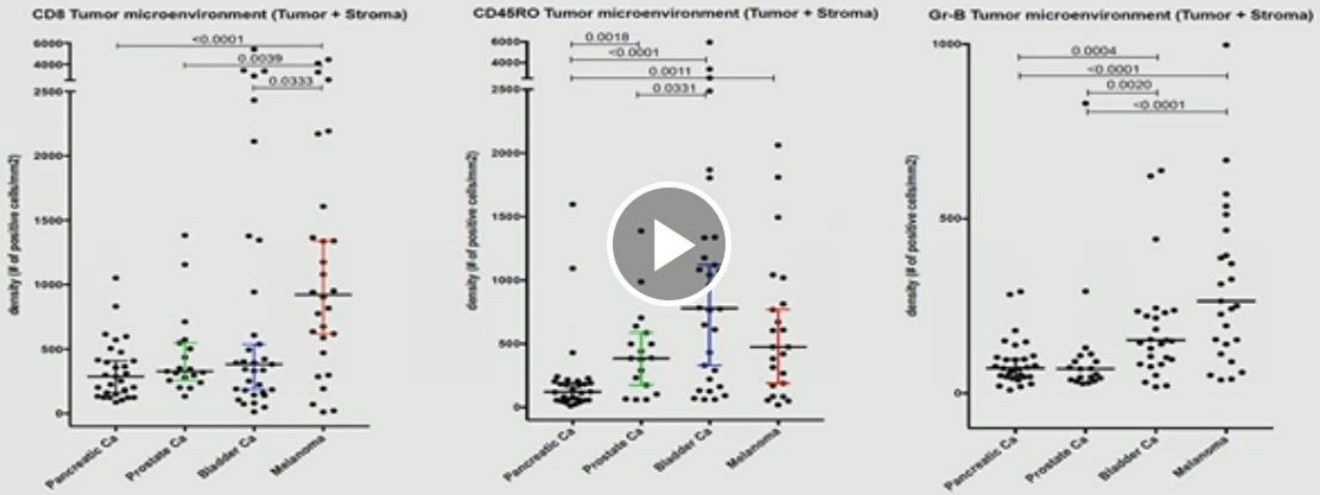


Figure 2: Radiographic progression-free survival in the (A) intention-to-treat population, (B) HRR mutation-positive subgroup, (C) wild-type HRR subgroup, and (D) partially characterised HRR status subgroup


Key Eligibility Criteria
• Progressive mCRPC
• First-line setting (chemotherapy naïve in mCRPC setting and NHA naïve; prior taxane allowed for mHSPC)
• ECOG PS 0-1
Stratification Factors
1. Metastases: bone only/visceral/other
2. Prior taxane treatment in mHSPC stage: yes/no
Randomization: 1:1, double-blind
Olaparib + Abiraterone (N=360)
Placebo + Abiraterone (N=360)
Objectives
Primary:
• rPFS by investigator assessment (BICR assessment as sensitivity analysis)
Key Secondary:
• Time to start of first subsequent anticancer therapy or death
• Time to pain progression
• Overall survival


Pilocytic astrocytoma
ALL
Medulloblastoma
AML
Kidney chromophobe
Thyroid
CLL
Neuroblastoma
Glioblastoma
Pancreas
Breast
Glioma low grade
Lymphoma B cell
Myeloma
Prostate
Ovary
Kidney papillary
Kidney clear cell
Liver
Uterus
Stomach
Head and neck
Cervix
Colorectum
Oesophagus
Lung small cell
Bladder
Lung adenocarcinoma
Lung squamous
Melanoma
Somatic mutation prevalence
(number mutations per megabase)
1,000
100
10
1.0
0.1
0.01
0.001

Immune infiltrates in untreated prostate cancer compared to other tumor types



Can we increase immune infiltration into prostate tumors?

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 33

Research Paper: Immunology

Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer

Table 2: Responding Patients*

Patient number	Date of cycle 1	PSA (ng/ml) baseline to nadir	Measurable Disease at Baseline	Best Radiologic Response	MSI	Prior Treatment for mCRPC
1	April 2015	70.65 → 0.08	Yes	PR	present	abi, enz
7	October 2015	46.09 → 0.02	No	N/A	n/a	abi, enz
10	January 2016	2502.75 → < 0.01	Yes	PR	absent	enz

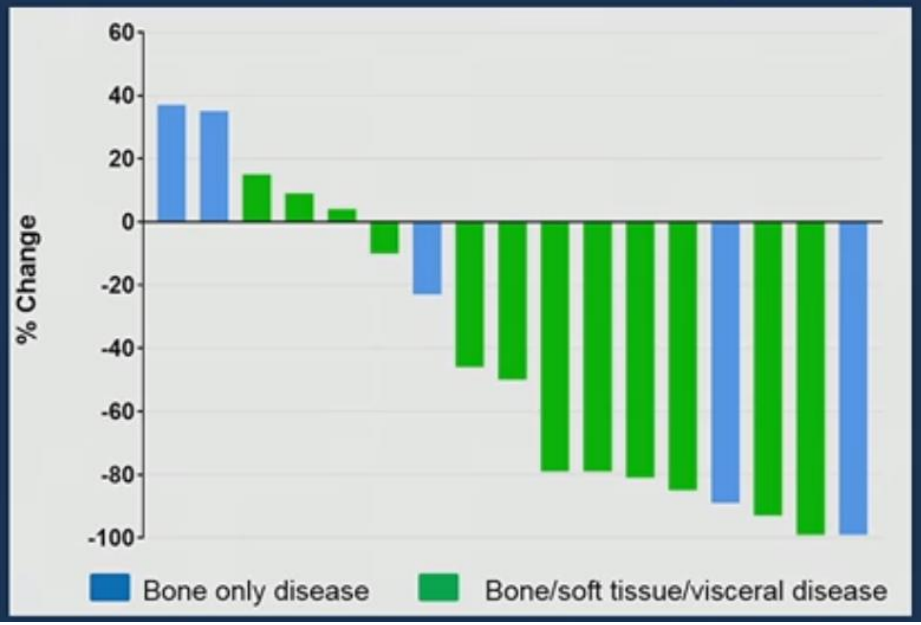
A Phase 2 of Study of Durvalumab Plus Olaparib for Advanced Metastatic Castration-Resistant Prostate Cancer (mCRPC) Regardless of DNA Damage Repair Mutational Status

Fatima Karzai, M.D.
Director, Prostate Cancer Clinic
Genitourinary Malignancies Branch
Center for Cancer Research
National Cancer Institute

Ravi A. Madan, Helen Owens, Lisa M. Cordes, Amy Hankin, Anna Couvillon, Erin Nichols, Marijo Bilusic, Mike L. Beshiri, Kathleen Kelly, Sunmin Lee, Min-Jung Lee, Akira Yuno, Jane B. Trepel, Jennifer Marte, Keith J. Killian, Paul S. Meltzer, Seth M. Steinberg, James L. Gulley, Jung-Min Lee*and William L. Dahut*(Senior Co-Authors)

PRESENTED AT: 2018 Genitourinary Cancers Symposium | #GU18

Maximum Decline in PSA (n=17)



Conclusions

- Practice-changing news concerned the nmCSPC setting

- Exciting perspectives are related to growing evidences about the activity of PARPi and iCKi

Do we have the chance

to change again the natural history of PC?